

Malignant hypercalcemia revealing a Diffuse large B cell lymphoma in a patient with a previous diagnosis of chronic myelomonocytic leukemia: an uncommon hematological coexistence

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Introduction

Hypercalcemia is one of the most frequent electrolyte disorders in patients with malignant diseases [1], presenting in about one quarter of these patients [2]. Hypercalcemia could result from osteolytic lesions or from production of humoral substances like parathyroid hormone-related protein (PTHrP) or uncontrolled synthesis and secretion of 1-25(OH)₂D₃ by the tumoral cell or macrophages. Within tumor-related etiologies, multiple myeloma, breast, lung, and kidney cancers are the most frequent [3,4]. In these diseases, hypercalcemia has been reported in 30% and 60% of patients with multiple myeloma and T-cell non-Hodgkin lymphoma [1]. However, hypercalcemia has only been reported in 7-8% of patients with B-cell non-Hodgkin lymphoma (NHL) and its prevalence and its prognostic value is unclear [2].

Case presentation

A 76-year-old male patient had been previously admitted to the cardiology department for replacement of a right ventricular lead on a double-chamber pacemaker. The patient had a history of transcatheter aortic valve implantation (TAVI) for bicuspid aortic valve (BAV III), with no complications following the operation. Fifteen days after this hospitalization, he was referred to the emergency department with progressive onset of dyspnea and desaturation to 85% on room air, associated with worsening of his general condition that has been progressive since his hospital discharge. He denied fever, chills, or night sweats. At the emergency department, blood tests revealed hyperkalemia at 5.2 mmol/L with preserved renal function and an inflammatory syndrome (C reactive protein 33 mg/L without hyperleukocytosis). Based on these test results, a chest CT scan was performed, revealing bronchopneumopathy predominantly in the right upper lobe segment, leading to the initiation of treatment with amoxicillin-clavulanic acid 1g every 8 hours.

The patient's past medical history was relevant for type 2 diabetes mellitus, Hashimoto's thyroiditis, heart failure due to dilated hypokinetic heart disease, atrial fibrillation, and chronic myelomonocytic leukemia (CMML-0) diagnosed in 2021. The patient had undergone TAVI in 2021 for severe aortic valve disease with tight aortic narrowing and 30% LVEF complicated by BAV III post-TAVI along with implantation of a double-chamber pacemaker. He had no drug or food allergies and his family history was noncontributory. He was on apixaban 5 mg twice daily, levothyroxine 25 ug per day, furosemide 40 mg daily, spironolactone 50 mg daily, bisoprolol 1.25 mg daily, ramipril 1.25 mg daily, insulin LISPRO, 4-4-4, and insulin glargine 32 units at night.

On physical examination, blood pressure was 110/70 mmHg, heart rate was 89 beats/minute, the patient was afebrile and oxygen saturation was 94% (two liters of oxygen with nasal goggles). He was alert and oriented.

Mucous membranes were moist and slightly discoloured. Heart sounds were regular without murmurs or rubs and, pulses were normal. Lung sounds were diminished with crackles in the right hemithorax. The abdomen was distended with a palpable splenomegaly.

Twenty-four hours after admission, the patient's general condition deteriorated abruptly, with the onset of drowsiness and psychomotor retardation. A broad biological workup was performed, revealing hypercalcemia at 4.18 mmol/L (normal value 2.20-2.70 mmol/L) associated with hyperphosphatemia (1.88 mmol/L), hyperuricemia (1455 μ mol/L), and a deterioration in renal function with GFR 37mL/min vs. 74 ml and creatinine at 153 vs. 86 μ mol/L. His albumin (33 g/L), magnesium, and ammonia were within normal range as well as coagulation tests and thyroid-stimulating hormone. Liver function tests were within the normal range except for lactate dehydrogenase (248 UI/L). In addition, we noted the development of hyperleukocytosis (11.4×10^9 /L), elevated C-reactive protein (58 mg/L), hemoglobin 9.1 g/dl, and platelets (87×10^9 /L). The electrocardiogram showed a known left bundle branch block and sinus tachycardia with anterior ST segment sub-shift and normal QT interval.

The patient was scoped and intensive hydration with physiological solution (2 liters), and treatment with calcitonin 100 IU every 6h, and zoledronic acid 3 mg were initiated. The patient was then transferred to the nephrology intensive care unit, where hyperhydration and antibiotics were continued. The patient underwent two sessions of hemodialysis, which normalized the serum calcium levels (2.54 mmol/L). He was then readmitted to our department for further etiological work-up of malignant hypercalcemia.

The remainder of the laboratory investigations showed diminished PTH at 4.6 (normal value 18.5-88 ng/L), phosphorus 1.78 mmol/L (normal value 0.87-1.50), vitamin 25-OH vitamin D at 8 μ g/L (normal value 30-80 μ g/L), 1-25-OH within normal range, and PTH-related protein (PTHrP) elevated 15.3 pmol/L (normal value <1.5 pmol/L). Angiotensin-converting enzyme and ferritin were within normal limits. We were therefore faced with a non-PTH-dependent hypercalcemia. In this clinical and biological context, a neoplastic origin was initially considered. A thoraco-abdominal scan revealed an extensive diffuse peritoneal carcinosis with perihepatic ascites, bilateral cardiophrenic pseudonodular tissue lesions probably of secondary origin, supra- and subdiaphragmatic adenopathies, and non-hypermetabolic splenomegaly probably associated with known CMML. Investigations were completed by PET scan describing an intense hypermetabolism of diffuse abdominopelvic peritoneal carcinosis, right pleural foci suspicious for malignancy associated with low-grade pleural effusion, multiple supra- and subdiaphragmatic adenopathies (lymphomatous or metastatic origin), and non-hypermetabolic splenomegaly linked with his known CMML. A biopsy of a peritoneal carcinosis nodule was performed.

Forty-eight hours later, the patient developed a severe hypotension associated with marbling and drowsiness. Laboratory blood tests revealed hyperleukocytosis (31.21×10^9 /L), polynuclear neutrophils (38.68×10^9 /L), monocytes 5.74×10^9 /L, and acute anuric renal failure (GFR 14 ml/min and creatinine 351 μ mol/L). Further testing revealed hyperkalemia associated with metabolic acidosis and hyperlactatemia. Corrected calcium was normal, phosphorus was 2.39 mmol/L (normal value 0.87-1.5), and uric acid was 1091 μ mol/L (normal value 208-428). He was transferred to the intensive care unit.

Upon admission to the intensive care unit, the patient underwent extra-renal purification with Prismaflex for acute renal failure secondary to spontaneous lysis syndrome as well as treatment with rasburicase. He was on dialysis for a total of 9 days and recovered urine production after the addition of diuretics. During his stay in intensive care, the patient received several probabilistic antibiotic treatments for a persistent fever. Antibiotics were finally suspended as all microbiological samples came back negative. The result of the biopsy confirmed the diagnosis of diffuse large-cell B lymphoma. The corticosteroid therapy that was initiated on admission was continued, along with two doses of rituximab. Then, in the absence of improvement, chemotherapy with vincristine and cyclophosphamide was initiated.

Despite aggressive treatment, the patient experienced a sudden episode of desaturation. Considering the lack of improvement and his poor prognosis, the decision of treatment escalation was not pursued. Active measures were discontinued and palliative support started. The patient expired shortly thereafter.

Discussion

Hypercalcemia is a relatively common clinical problem. Among all causes of hypercalcemia, primary hyperparathyroidism and malignancy are the most common, accounting for greater than 90 percent of cases [5]. It is often not difficult to differentiate both conditions, as malignancy is usually clinically evident by the time hypercalcemia appears, and patients with hypercalcemia of malignancy usually have higher calcium concentrations and are more symptomatic than those with primary hyperparathyroidism [5].

Our patient presented with a malignant hypercalcemia with low parathyroid hormone and normal calcitriol levels along with hyperphosphatemia and increased rPTH. After performing a thoraco-abdominal scan, our first hypothesis was a solid tumor but the origin was difficult to determine. The presence of an extensive abdominal calcinosis and adenopathies prompted us to initially suspect a gastrointestinal origin. To establish the diagnosis, and after medical discussion, a peritoneal carcinosis nodule biopsy was performed and found to be consistent with diffuse large-cell B lymphoma once the patient was already in the intensive care unit. This result was not expected as calcitriol was normal, he presented a non-hypermetabolic splenomegaly linked with his known CMML and rPTH was increased.

Diffuse large B cell lymphoma (DLBCL) is the most frequent subtype of lymphoma in western countries [6,7]. However, the prevalence of hypercalcemia and its prognostic value remain unclear. Previous studies in NHL reported a prevalence of hypercalcemia ranging from 7-14%, but these studies included different subtypes and often considered the development of hypercalcemia during the entire disease course and not only at diagnosis. [6] In contrast, Gauchy et al conducted a study showing that hypercalcemia is not uncommon in newly diagnosed DLBCL and was associated with a poor clinical outcome [6]. Abadi et al also reported a prevalence of 18% in the novo DLBCL patients from two referral centers [2].

Regarding the etiology of hypercalcemia, some patients with DLBCL may present with hypercalcemia secondary to hyperparathyroidism and not lymphoma related. Previous studies have shown that levels of calcitriol are often increased in these patients [1,2], but this was not the case in the patient reported. Notably, it is rare to find ectopic secretion of PTH by a neoplastic clone as the cause of hypercalcemia [2]. The presence of low levels of calcitriol and increased levels of PTHrP made us search initially for a solid tumor delaying the diagnosis and therefore the specific treatment. Hypercalcemia secondary to the production of PTHrP as seen in our case is unusual [1,2], with only limited cases reported.

Another intriguing clinical feature of this case was the development of Diffuse large B cell lymphoma in a patient previously diagnosed with CMML. CMML arises from the combination of hypersensitivity of myeloid precursors to granulocyte-macrophage colony-stimulating factor, myeloid cell dysplasia, and ineffective hematopoiesis [8]. There are only a few cases in which CMML is associated with other hematological conditions, including lymphoproliferative diseases such as monoclonal gammopathy of uncertain significance (MGUS), monoclonal B-cell lymphocytosis (MBL), multiple myeloma (MM), and non-Hodgkin T- and B-cell lymphomas as in this case [8,9]. CMML is an uncommon myeloid disorder that is rarely associated with NHL[8]. Romano et al described a case with synchronous chronic myelomonocytic leukemia and diffuse large b-cell lymphoma[8].

Conclusions: The etiologic diagnosis of hypercalcemia is a challenge in clinical practice, especially when the initial results are not in favor of what is described in the literature, often leading to a delay in diagnosis, treatment, and poorer prognosis. Hypercalcemia in newly diagnosed patients with diffuse large B lymphoma may be due, albeit rarely, to PTHrP production and is associated with a worse prognosis. Coexistence of chronic myelomonocytic leukemia and diffuse large B lymphoma is unusual.

Conflicts of Interests: The Authors declare that there are no competing interests.

Patient Consent : Authors obtained the consent from the patient's family.

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